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1. Your reference

PAC/GB1004

2. Patent application number
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9813031.3

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3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

ReGen Biotech Limited

Patents ADP number *(if you know it)*

If the applicant is a corporate body, give the country/state of its incorporation

Cliffords Inn
Fetter Lane
London EC4A 1AS
United Kingdom

7448911002

4. Title of the invention

DIETARY SUPPLEMENT

5. Name of your agent *(if you have one)*

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

A. A. THORNTON & CO.

Northumberland House,
303 - 306 High Holborn,
London WC1V 7LE

Patents ADP number *(if you know it)*

75001

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body.
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Description	8
Claim(s)	0
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Priority documents	N/A
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Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	-
Request for preliminary examination and search *(Patents Form 9/77)*	-
Request for substantive examination *(Patents Form 10/77)*	-
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11. I/We request the grant of a patent on the basis of this application.

Signature A. A. THORNTON & CO. Date 16 June 1998

12. Name and daytime telephone number of person to contact in the United Kingdom

Philip A. Curtis - 0171-405 4044

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DIETARY SUPPLEMENT

The present invention relates to a dietary supplement and, in particular, to a dietary supplement for promoting the functioning of the immune system.

When a baby is born, its immune system is normally dormant and non-functioning but, as the baby grows, the immune system becomes active. There has recently been a hypothesies that mother's colostrum contains components which contribute to the awakening and development of the immune system. One particular such component is called colostrinin. It is found in ovine and human colostrum and it has recently been classified as a new cytokine.

As a result of our studies, we have found that the administration of colostrinin to an infant may be of singular importance to the full development of the immune system, and that it is possible that an infant fed solely on bottle formula milk preparations may, as a result of not receiving colostrinin, have a poorly developed immune system. An imperfectly developed immune system can lead to the development of serious diseases such as atopic allergies including, for example, as asthma and skin allergies. There have even been reports that a reduced function of the immune system can lead to senility in old age and, possibly, to Alzheimer's disease.

It is impractical to solve this problem by trying to take steps to ensure that all infants are breast fed, because some mothers are physically unable to breastfeed, and others may not be able to breastfeed because they are undergoing treatment themselves and are taking drugs which should not be passed on to the baby through breast milk. Also, in some areas of the world, there is a social stigma attached to breastfeeding.

We have now devised a dietary supplement formula for promoting the correct functioning of the immune system. The supplement can be given to non-breast fed infants, for example by inclusion in their baby formulas or powdered milk feed. It can also be given to breast-fed infants, and to children and adults at any time of their life. Thus, the invention provides a way of treating an individual

with a view to promoting their immune system whether or not they have been breast-fed, and whatever their state of health.

The dietary supplement of the present invention comprises colostrinin in combination with at least one of, and preferably with both of, lactoferrin and selenium. We have found that this combination of substances exhibits synergism.

By dietary supplement we mean a preparation or formulation which is added to or otherwise included in a person's normal diet, and is present in addition to the normal diet. Thus, for example, a dietary supplement of the invention can be:

(a) in the form of a liquid or solid, eg. powder or as individual dosage units such as baby food formula, tablets or the like to be added to food or drinks, or taken with them;

(b) added to a foodstuff during its preparation, such as added to powdered milk feed for babies or otherwise included in children's and adults' foodstuffs.

By dietary supplement we do not intend to embrace foodstuffs per se that may naturally contain the components of the supplement according to the invention.

The lactoferrin, selenium and colostrinin present in the food supplement of the invention can each be of natural or synthetic origin, eg. produced by recombinant DNA technology. The supplements will normally also include a physiologically acceptable diluent or carrier such as is appropriate to the particular use intended.

In a preferred embodiment, the selenium is in the form of a physiologically acceptable complex with protein for example bound to Lactobacillus acidophilus, gluathione peroxidase or yeast protein. Furthermore, the selenium protein complex is preferably human and may be from a recombinant or natural source. Selenium is known to be a weak inducer of the cytokines and in particular of gamma interferon. It is particularly preferred that the selenium be present in the dietary supplement in the form of selenium rich proteins rather than as a salt, for example, since when administered as for example selenium picollinate, it is

generally not fully utilised by the body.

The term "Colostrinin", as used herein refers to a polypeptide which, in its natural form, is obtained from any mammalian colostrum. Colostrinin is sometimes known as "colostrinine", and has the following properties:

(i) it has a molecular weight in the range 16,000 to 26,000 Daltons;

(ii) it is a dimer or trimer of sub-units each sub-unit having a molecular weight in the range 5,000 to 10,000 Daltons, preferably 6,000 Daltons;

(iii) it contains proline, and the amount of proline is greater than the amount of any other single amino acid.

Colostrinin, and also the sub-units making up the Colostrinin, are non-polar.

The isolation of, and characterisation of, ovine colostrinin is discussed in Janusz, Maria et al, "Proline-Rich Polypeptide (PRP) - an Immunomodulatory Peptide from Ovine Colostrum", Archivum Immunologiae et Therapiae Experimentalis, vol. 41, no. 5-6, 1993, pages 275-279. The colostrinin used in the food supplement of the invention may be derived naturally from any mammalian source, such as humans, bovine, goats or sheep. Alternatively, the colostrinin may be made synthetically, for example, by recombinant DNA techniques. The colostrinin need not necessarily be in a pure form but may instead be, for example, partially purified as, for example, I_gG-colostrinin complex, or in a crude preparation form like whey, so long as the form is physiologically acceptable.

The source of the lactoferrin is also not critical but it should preferably be bovine, ovine or human origin (or derived therefrom). Most preferably, human lactoferrin and/or human recombinant lactoferrin is used.

The preferred amounts of each ingredient per unit dose of the dietary supplement is as follows: colostrinin from about 12½ micrograms to about 200 micrograms; lactoferrin from about 10 micrograms to about 100 milligrams; and selenium, in the form of seleno-cysteine, from about 2.5 to about 100 micrograms.

The preferred dosage of the dietary supplement of the invention is

one preferred unit dose per day.

The dietary supplement of the invention may further include other biologically active substances such as cytokines present in colostrum other than colostrinin, and hormones. For example, the supplement may include a natural cytokine preparation containing members of the interferon family, interleukin 1-∝, interleukin 1-3, interleukin-6, 8, 10, 12, 16, tissue necrosis factor ∝, G-CSF, M-CSF, TGF∝ and TGFβ.

The physiologically acceptable carrier of the dietary supplement of the present invention is chosen to be suitable for the intended use. Examples of suitable carriers include for example a solution of the hydrolysates of β casein in the form of 6.000 m.w. peptides, phosphate buffered saline (PBS), and whey.

The most preferred route for administering a dietary supplement of the invention is oral, especially in a form in which the supplement is maintained in contact with the oral and/or pharyngeal and/or intestinal tract mucosa. One preferred form is that of a baby food formula. Another preferred form is that of a lozenge, designed to be dissolved in the mouth. In the lozenge or other form, the dietary supplement may further include various flavouring or sweetening agents such as sucrose, mannose, lactose, maltose, trehalose, cold water soluble starch or other such ingredients known in the art.

As will be understood, the food supplement of the invention can be in a number of other forms such as powders, tablets, or liquid drinks and baby formulas. When in powder form, they can be added to a foodstuff such as, for example, a powdered milk formulation (or cheese or indeed any other foodstuff). The source of the milk is not important and may, for example, be cow, goat or sheep. The powdered milk formulation may be made up with a liquid to form a drink.

In another form, the dietary supplements of the invention can be included in a cheese. The source of milk forming the base of the composition to form the cheese is not important, but may include cow, goat or sheep.

The dietary supplement of the invention can also be added to the whey of goat, cow or sheep milk origin which whey may be obtained during

cheese production. The whey product containing the dietary supplement may be consumed as a drink.

In a further aspect of the present invention, there is provided the use of colostrinin in combination with lactoferrin or selenium, and preferably in combination with lactoferrin and selenium, in the manufacture of a medicament for bringing about an improvement in a individual's immune system.

The dietary supplement of the present invention can result, in adults, in an increase in energy and an apparent increase in clarity of thinking.

The dietary supplement of the invention should not be used for more than 21 days continuously. This is because the phenomenon of tachyphylaxis may otherwise be induced. Tachyphylaxis is the gradual loss of an individual's capability to synthesise cytokines. In this situation an adverse reaction may be experienced. Induction of tachyphylaxis may be avoided by discontinuing the use of the dietary supplement of the invention after 21 days for a period of not less than 3 weeks. Following this brief pause, a new cycle of use can be initiated.

According to another aspect of the present invention there is provided a method of stimulating an individual's immune system, which method consists essentially of administering a dietary supplement of the present invention in unit dosage form, preferably each day for 21 consecutive days.

In order that the invention may be more fully understood, the following Examples are given by way of illustration only.

Examples

Example 1

Lozenge Formulation

The composition of a lozenge formulation of an example of the dietary supplement of the invention per unit dose is as follows:

Ingredient	Amount
Sucrose, lactose or trehalose and/or	25 mg
Cold-water-soluble starch	42 mg
Phosphate Buffered Saline	(if required)

Natural colostrinin	100 μg
Selenium (metalloprotein) or other seleno-cysteine-containing proteins	5 μg
Purified recombinant human lactoferrin	10 mg

Example 2

Method of manufacture of lozenge formulation

A starch gel-based lozenge containing colostrinin, lactoferrin and selenium is prepared by combining 150 g sucrose, 550 ml phosphate 0.15 mm buffered saline, and 250 g of cold-water-soluble starch such as that described in U.S. Patent 4,465,702, heating the mixture with stirring to a temperature of 75°C, cooling the mixture to 30°C and thereafter blending into the paste-like mass with 50 ml PBS containing 3 mg purified human colostrinin, 4.5 mg selenium (rich protein) and 300 mg purified recombinant human lactoferrin. The mixture is then formed into multiple portions of 5 to 10 grams each, which set upon standing under drying conditions to a starch candy gel-like consistency. The lozenges thereby produced can be administered to a patient singly or in combination. The patient is instructed to hold the lozenge in his mouth until it is completely dissolved to release the components for contact with the oral mucosa.

Example 3

Powdered Milk Formulation

A formulation for feeding to a baby post weaning from mother's milk, is:

Proprietary milk powder (e.g. Sma , White by Sma Nutrition, Maidenhead, U.K. *)	4g **
Natural ovine colostrinin	150μg
Selenium (bound to lactobacillus acidophilus)	8.25μg (free selenium)
Human Recombinant Lactoferrin	1.0 mg

* Sma ingredients quoted as lactose, skimmed milk powder, vegetable oils, emulsifier (soya lecithin), potassium bicarbonate, vitamin C, taurine, ferrous sulphate, zinc sulphate, cytidine-5'-monophosphate, disodium uridine-5'-monophosphate, vitamin E, adenosine-5'-monophosphate, niacin, disodium inosine-5'-monophosphate, disodium guanosine-5'-monophosphate, pantothenic acid, vitamin A, copper sulphate, thiamin, vitamin B, riboflavin, beta-carotene, manganese sulphate, folic acid, vitamin K, potassium iodide, biotin, vitamin D, vitamin B.

** Follow manufacturer's instructions for dosage guide e.g. weight 6.5 kg, approximate age of baby 4 months, 7 level scoops in 200 ml cooled (freshly boiled) water.

Example 4

Baby Food Formulas

The following formulations may be used for very young babies:

Formulas for new born 1 - 7 days old:

Natural Colostrinin (antibody - colostrinin complex)	50 μg per serving.
Lactoferrin (human recombinant or natural bovine)	100 μg per serving.

Formulas for 8-14 days old babies:

Natural colostrinin	5.0 μg per serving.
Lactoferrin	100 μg per serving.
Selenium in form of seleno-cysteine	1.0 μg per serving.

Formulas for 15-30 days old babies.

Natural colostrinin	None
Lactoferrin	50 μg per serving.
Selenium	0.5 μg per serving.

Formulas for 31-45 days old babies.

Natural colostrinin complex	10 μg per serving.
Lactoferrin	50 μg per serving.
Selenium	0.5 μg per serving.

It will be appreciated that modifications may be made to the invention described above.